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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/897,390	07/21/97	LA VAIL M	REG-32

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GAIL M KEMPLER
REGENERON PHARMACEUTICALS INC
777 OLD SAW MILL RIVER ROAD
TARRYTOWN NY 10591

EXAMINER	
HAYES,R	
ART UNIT	**PAPER NUMBER**
1645	7

DATE MAILED: 10/27/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/897,390	Applic(s) LaVail et al
	Examiner Robert C. Hayes	Group Art Unit 1645

☒ Responsive to communication(s) filed on *Jun 4, 1999* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-35* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-35* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of Group I in Paper No. 6 is acknowledged.

The traversal is on the ground(s) that because "the subject matter of each group... is readily searched co-extensively without undue burden on the Examiner". This is not found persuasive because the nucleic acid molecules required in the assay method of Group II requires chemically and physically distinct from the treatment method requiring neurotrophic protein molecules of Group I. Additionally, albino rat eyes are requierd in the assay method of Group II, in contrast to any mammal suffereing retinal neuronal degeneration of Group I, as previously made of record. Moreover, each of these groups have acquired a separate status in the art as shown by their different classification (i.e., Group I versus Group II). Therefore, the non-coextensiveness of the search and examination for each group would constitute an undue burden on the examiner to search and consider each of the separable groups with their recognized divergent subject matter, and for the reasons made of record. The requirement is still deemed proper and is therefore made FINAL.

Claims 36-38 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to non-elected inventions, the requirement having been traversed in Paper No. 6.

This application contains claims 36-38 drawn to an invention nonelected with traverse in Paper No. 6. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 112

2. Claims 1-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of increasing survival of embryonic chick ciliary neurons with BDNF, CNTF, FGF, TNF, IL-1, NT-3 and IGF-2, does not reasonably provide enablement for any *in vivo* method for generically treating any neurodegenerative disease state with structurally uncharacterized neurotrophic factor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification proposes a method of "treating" neurological disorders in a patient with a "therapeutically effective amount" of BDNF, CNTF, FGF, TNF, IL-1, NT-3 and IGF-2. However, no disclosure is provided in the specification on how to "treat" any neurological disorder, nor on how to assess *in vivo* "administration of an effective amount of "BDNF, CNTF, FGF, TNF, IL-1, NT-3 and IGF-2. Nor is it disclosed how BDNF, CNTF, FGF, TNF, IL-1, NT-3 and IGF-2 can "therapeutically and effectively" treat any of the unique disease pathologies claimed, or how any model system containing any neural pathways reminiscent of that found *in vivo* can be effectively treated with such.

First, the state of the art is such that numerous problems exist concerning effective "treatment" of neurological disorders, because the mechanism resulting in neural degeneration by one causative factor is not predictive of the mechanism/treatment of a neurological disorder for a different causative factor. Problems also encountered before assessing whether treatment with an effective amount of BDNF, CNTF, FGF, TNF, IL-1, NT-3 and IGF-2 reasonably occurs within the CNS or PNS are that neuronal cell damage often results in cell death, and that "administration" of neurotrophic factors to treat neurons requires solutions to not only bypassing the blood-brain barrier when treating CNS disorders but to selectively target responsive cells, if known, with enough neurotrophic factor to elicit any response (i.e., through specific receptor binding). In other words, "effective" *in vivo* administration, as it relates to treating any neuronal cell type/disease state with any protein, requires that one skilled in the art must know how, when or where the proposed invention is to be administered. In contrast, the instant specification has failed to disclose how these parameters are to be determined, what specific neuronal populations are responsive to the BDNF, CNTF, FGF, TNF, IL-1, NT-3 and IGF-2 polypeptides of the instant invention, how a similar disclosed method was practiced in the art with a different agent, or to provide even a single *in vivo* working example of the claimed method. In contrast, Sendtner (see Barinaga, 1994) found that the neurotrophic factor CNTF is quickly taken up and degraded by the liver with a half life of 3 minutes (i.e., as it especially relates to claims 39-40). Moreover, in this same publication it was reported (same column on pg. 773) that Regeneron's Phase III study on CNTF to treat ALS resulted in a substantial number of those receiving CNTF

having not only serious side effects, but having actually fared worse on measures of muscle strength than did patients receiving placebos. Thus, because it is unclear how one could administer an effective dose of any CNTF-derived neurotrophin, and by analogy any BDNF, CNTF, FGF, TNF, IL-1, NT-3 and IGF-2 polypeptide, for a sufficient time period to elicit any measurable response, because it is unknown or disclosed what route of administration is effective for using any BDNF, CNTF, FGF, TNF, IL-1, NT-3 and IGF-2 polypeptide, or any "second neurotrophic factor" to "treat" any degenerating neuron *in vivo*, because it is unknown what parameters are required to be assayed in order to determine when, or if, the instant invention is "effective" in treating any "disorder", and because it cannot be successfully extrapolated from the limited *in vitro* tissue cultures disclosed whether the skilled artisan has successfully practiced Applicant's invention, it would require undue experimentation for the skilled artisan to discover how to make and use Applicants' invention, as currently claimed.

Second, in order to practice the full scope of the invention, regeneration of the damaged axons in these neurodegenerative disease states are required, in order to "effectively treat", or "retard or halt neuronal degeneration", as claimed. However, without functional synaptogenesis, there is no functional regeneration, and therefore, no expectation that regeneration/effective treatment of any neurological disorder or disease is possible; especially as it relates to the recited disease states claimed, in which neurons otherwise die. Regeneration does not occur either because processes fail to grow the necessary distance, they are in competition with other nearby neuronal processes not derived from the affected nerve, astrocytic scarring blocks axonal

elongation, or because of misdirected axonal growth (e.g., see Jackowski, pgs. 309-310). In other words, neurons do not regenerate in the CNS (e.g., see Jackowski, pg. 305, last *pp*; as it especially relates to claims 31, 34-43). In contrast, the instant description fails to provide any guidance on how to prevent diseased neurons from degenerating, or how to prevent any neuron from dying; nor how any of the unique disorders recited in the claims, each with their unique etiology, can be effectively treated, especially within the CNS; nor how to assay such *in vivo*. For example, only the outer segment of photoreceptor cells can effectively be treated when damaged, versus any more severe type of neuronal damage resulting in cell death (see Rapp, pg. 971, Fig. 2; e.g., as it relates especially to claims 26-28 & 53-54); thereby, being consistent with the unpredictable state of the art as discussed above. Thus, because the instant specification discloses no *in vivo* assays for determining when, or if, the Applicant's invention works *in vivo,* or when any of the claimed disease states were "retarded", "slowed/halted" or "treated", the claims, as such, merely constitute an invitation to experiment how to use the invention.

Third, although the specification does list various "disorders" found within the nervous system, the specification fails to describe how the instant invention can be used to treat these disorders with an effective amount of any BDNF, CNTF, FGF, TNF, IL-1, NT-3 and IGF-2 polypeptide, in that no disease state is known, or disclosed, that is dysfunctional due to altered expression of BDNF, CNTF, FGF, TNF, IL-1, NT-3 and IGF-2. For example, claim 36 recites treatment of ALS, which involves cholinergic motoneuron dysfunction, whereas claim 35 recites treatment of Parkinson's Disease, which involves dysfunction of dopamineregic neurons.

Importantly, neither of these disorders are anatomically or physiologically equivalent with the single *in vitro* embryonic chicken ciliary neuronal example provided in the specification. Overall, the specification fails to teach how any putative neurotrophic factor, including BDNF, CNTF, FGF, TNF, IL-1, NT-3 and IGF-2, is associated with any of the claimed neuropathological conditions, which include cell death issues that additionally characterize Parkinson's disease (i.e., as it relates to claim 35), ALS (i.e, as it relates to claims 33, 36 & 41), or peripheral neuropathy (i.e., as it relates to claims 32-33), and therefore, cannot be treated, by definition. Further, it is not known, or disclosed, at what point during the course of the disease that treatment is recommended, nor how the severity of symptoms are related to the efficacy of BDNF, CNTF, FGF, TNF, IL-1, NT-3 and IGF-2 or any neurotrophic factor; thereby, requiring undue experimentation to discover how to make and use Applicant's invention.

Lastly, the name BDNF, CNTF, FGF, TNF, IL-1, NT-3 and IGF-2 alone (e.g., as it is defined on page 9 of the specification) encompasses any random mutation, addition, substitution, deletion, fragment or any biologically functional equivalent of any BDNF, CNTF, FGF, TNF, IL-1, NT-3 and IGF-2 related polypeptide; thereby, providing no structural characterization and little functional characteristics for how to make the required BDNF, CNTF, FGF, TNF, IL-1, NT-3 and IGF-2 polypeptides to practice the claimed method. The specification further fails to define what specific amino acids are critical for any neurotrophic-related function, especially for a factor that normally functions on cardiac tissue. In addition, the skilled artisan would reasonably expect that random mutations to any protein (i.e., as encompassed by the current claim language) would

result in inactive BDNF, CNTF, FGF, TNF, IL-1, NT-3 and IGF-2 related protein, and therefore a method that does not work. For example, Rudinger states on page 3 that "it is impossible to attach a unique significance to any residue in a sequence. A given amino acid will not by any means have the same significance in different peptide sequences, or even in different positions of the same sequence". Rudinger then states on page 6 that "the significance of particular amino acid sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study". Therefore, the lack of guidance provided in the specification as to what minimal structural requirements are necessary for "knowing how to make or use" any BDNF, CNTF, FGF, TNF, IL-1, NT-3 and IGF-2-related polypeptide does not in itself provide sufficient guidance on what peptides could be made which retains the desired function of the instant invention, because any such random mutation within a BDNF, CNTF, FGF, TNF, IL-1, NT-3 and IGF-2 polypeptide would be predicted to adversely affect the three-dimensional conformation of the polypeptide, without requiring undue experimentation to determine otherwise.

In summary, the specification provides insufficient guidance to practice the full scope of the invention, in that it is unknown, nor disclosed, how to "effectively administer" any claimed peptide into the CNS of a subject, nor how any of the unique disorders recited in the claims, each with their unique etiology, can be "effectively treated"; especially within the CNS. Nor is it known or disclosed how to assay when, or if, the instant invention works *in vivo,* or what parameters could be assayed for determining such in this very unpredictable art; thereby, requiring

undue experimentation to determine such. Thus, because the instant specification discloses no *in vivo* assays for determining how, when, or if, the Applicant's invention works *in vivo,* or when any of the claimed disease states are "treated", the claims, as such, merely constitute an invitation to experiment how to use the invention.

3. Claims 1-35 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete because no recitation is included that defines when "treatment of neuronal degenerative diseases..." is accomplished, as recited in the preamble.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (703) 305-3132. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

RCH

Robert C. Hayes, Ph.D.
October 22, 1999